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**(54) PROCESS FOR THE PREPARATION OF (2R, 3S)-3-AMINO-1,2-OXIRANE**

**VERFAHREN ZUR HERSTELLUNG VON (2R, 3S)-AMINO-1,2-OXIRAN**

**PROCEDE DE PREPARATION DE (2R, 3S)-3-AMINO-1,2-OXIRANE**

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(56) References cited:  
**EP-A- 0 657 446 WO-A1-99/38855**  
**JP-A- 6 206 857 US-A- 5 475 013**

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• **ROMEO S ET AL: "STEREOSELECTIVE  
SYNTHESIS OF PROTECTED AMINO ALKYL  
EPOXIDES" TETRAHEDRON LETTERS,  
ELSEVIER SCIENCE PUBLISHERS,  
AMSTERDAM, NL, vol. 35, no. 28, 1994, pages  
4939-4942, XP000961134 ISSN: 0040-4039**

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## Description

## TECHNICAL FIELD

**[0001]** The present invention relates to a process for producing (2R,3S)-3-amino-4-phenylbutane-1,2-epoxide (hereinafter also referred to as 3-amino-1,2-oxirane), which is useful as an intermediate for the production of an HIV protease inhibitor.

## BACKGROUND ART

**[0002]** The processes so far known for producing said (2R,3S)-3-amino-1,2-oxirane comprise starting with L-phenylalanine, reducing the carboxyl group thereof to an alcohol function, reoxidizing the same to an aldehyde function, and thereafter 1) directly causing formation of the epoxide using a dimethylsulfonium methylide (J. Org. Chem., 1985, 50, 4615; J. Med. Chem., 1992, 35, 2525), 2) converting the aldehyde to the corresponding olefin by the Wittig reaction and epoxidizing the olefin using m-chloroperbenzoic acid (J. Org. Chem., 1987, 52, 1487; J. Med. Chem. 1992, 35, 1685), 3) reacting the aldehyde with trimethylsilylmethylmagnesium chloride, converting the resulting trimethylsilyl alcohol to the corresponding olefin by treatment with trifluoroboron and, as in the method 2) mentioned above, conducting epoxidation using m-chloroperbenzoic acid (EP 0532-466 A2, US 5,514,814) or 4) converting L-phenylalanine to the diazoketone form, degrading the same with hydrochloric acid, reducing the resulting  $\alpha$ -ketone with NaBH<sub>4</sub> and treating the resulting chlorohydrin with a base to give the epoxide (J. Med. Chem., 1994, 37, 1758), among others. EP 0 657 446 A1 discloses a process for producing optically active erythro-3-amino-1,2-epoxy compounds via an optically active threo-3-amino-2-sulfonyloxy butyrate derivative.

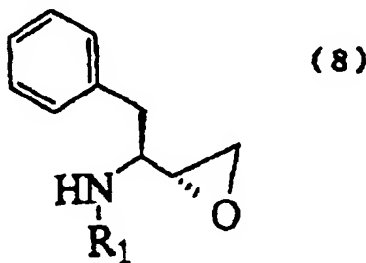
**[0003]** Meanwhile, there is no precedent technology for producing (2R,3S)-3-amino-1,2-oxirane compounds represented by the general formula (8) starting with a (2S,3S)-3-amino-1-chloro-2-hydroxy-4-phenylbutane compound or a (2S,3S)-3-amino-1,2-oxirane compound as in the process of the present invention.

**[0004]** Referring to the above known processes, the process 1) is disadvantageous in that it is necessary to use the sulfur compound in large amounts in the step of epoxide formation, the methods 2) and 3) are disadvantageous in that it is necessary to use the peroxide, which is explosive, in large amounts, and the method 4) is disadvantageous in that it is necessary to handle the diazo compound, which is also explosive, and, in addition, the selectivity toward the desired (2R,3S)-chlorohydrin in NaBH<sub>4</sub> reduction is low. Thus, every process comprises a step undesirable from the viewpoint of commercial scale practicing.

## SUMMARY OF THE INVENTION

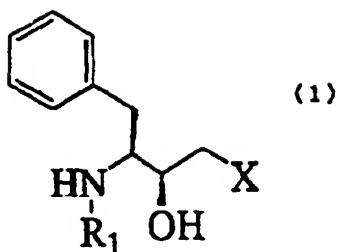
**[0005]** In view of the problems mentioned above, the present inventors made intensive investigations in an attempt to develop a process for producing a (2R, 3S) -3-amino-1,2-oxirane compounds which can be carried out efficiently and on a commercial scale and, as a result, succeeded in developing a novel process for production which starts with a (2S,3S)-3-amino-1-chloro-2-hydroxy-4-phenylbutane compound or a (2S,3S)-3-amino-1,2-oxirane compound and involves three steps, namely acyloxylation, sulfonate ester formation and treatment with a base.

**[0006]** Thus, the present invention relates to a process for producing (2R,3S)-3-amino-4-phenylbutane-1,2-epoxide compounds represented by the general formula (8):

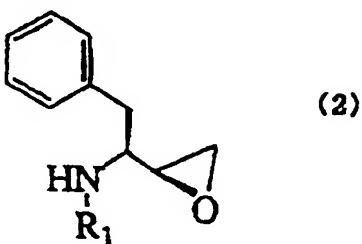


wherein R<sub>1</sub> represents an amino-protecting group, which comprises

treating a (2S,3S)-3-amino-1-halo-2-hydroxy-4-phenylbutane compound represented by the general formula (1) or a (2S,3S)-3-amino-4-phenylbutane-1,2-epoxide represented by the general formula (2):



wherein  $R_1$  is as defined above and X represents a halogen atom,



wherein  $R_1$  is as defined above,

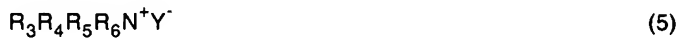
with a carboxylic acid quaternary ammonium salt represented by the general formula (3) or a carboxylic acid metal salt represented by the general formula (4):



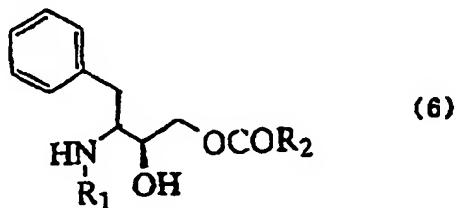
wherein  $R_2$  represents an alkyl, aryl or aralkyl group and  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  may be the same or different and each independently represents an alkyl or aralkyl group,



wherein  $R_2$  is as defined above and M represents a metal atom, and a quaternary ammonium salt represented by the general formula (5):

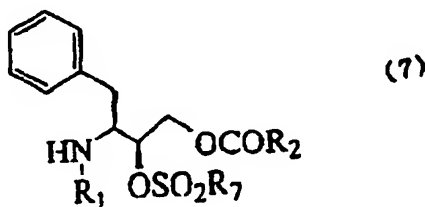


45 wherein  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are as defined above and Y represents a halogen atom, to give a (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phenylbutane compound represented by the general formula (6):



wherein  $R_1$  and  $R_2$  are as defined above,

further treating said (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phenylbutane compound with a sulfonic acid halide in the presence of an organic base to give a (2S,3S)-1-acyloxy-3-amino-2-sulfonyloxy-4-phenylbutane compound represented by the general formula (7) :



wherein  $R_1$  and  $R_2$  are as defined above and  $R_7$  represents an alkyl, aryl or aralkyl group, and furthermore treating said (2S,3S)-1-acyloxy-3-amino-2-sulfonyloxy-4-phenylbutane compound with an inorganic base.

**[0007]** The (2S, 3S)-3-amino-1-halo-2-hydroxy-4-phenylbutane compound can be synthesized, for example, by N-protection of L-phenylalanine, which is a naturally-occurring and inexpensive substance, followed by esterification, and stereoselective reduction of the haloketone resulting from chain extension (Japanese Kokai Publication Hei-08-823756).

#### BEST MODES FOR CARRYING OUT THE INVENTION

**[0008]** The starting compound in the present process is the above-mentioned (2S,3S)-3-amino-1-halo-2-hydroxy-4-phenylbutane compound of the general formula (1) or (2S,3S)-3-amino-4-phenylbutane-1,2-epoxide compound of the general formula (2). In the formulas,  $R_1$  represents an amino-protecting group in common use, such as a methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, acetyl, benzoyl or chloroacetyl group, desirably a t-butoxycarbonyl or benzoyloxycarbonyl group, and X represents a halogen atom such as a chlorine or bromine atom.

**[0009]** The acyloxylating agent to be used in the above process is the above-mentioned carboxylic acid quaternary ammonium salt of the general formula (3), or the carboxylic acid metal salt of the general formula (4) plus the quaternary ammonium salt of the general formula (5). In the formula (3),  $R_2$  represents an alkyl, aryl or aralkyl group. The alkyl group is, for example, methyl, ethyl, propyl, isopropyl, butyl or isobutyl. The aryl group is, for example, phenyl or tolyl. The aralkyl group is, for example, benzyl. A methyl group is preferred as  $R_2$ , however. In the formula (3), M specifically includes, among others, lithium, sodium, potassium, magnesium and calcium, and is preferably sodium or potassium.  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  each independently represents an alkyl or aralkyl group. The alkyl group includes, among others, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. The aralkyl group is, for example, benzyl. Among these, butyl is preferred. Y is a halogen atom, such as a chlorine or bromine atom.

**[0010]** In the general formula (7) representing the sulfonate ester,  $R_7$  represents an alkyl, aryl or aralkyl group. The alkyl group is, for example, methyl or ethyl. The aryl group is, for example, phenyl, p-methylphenyl or p-nitrophenyl. The aralkyl group is, for example, benzyl. Among them, methyl is preferred.

**[0011]** In accordance with the present invention, the above (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phenylbutane compound (6) is first derived from the (2S,3S)-3-amino-1-halo-2-hydroxy-4-phenylbutane compound (1) or (2S,3S)-3-amino-1,2-oxirane compound (2) by treatment with the carboxylic acid quaternary ammonium salt (3), for example tetrabutylammonium acetate, or with the carboxylic acid metal salt (4) and quaternary ammonium salt (5), for example calcium acetate or sodium acetate, and tetrabutylammonium chloride or tetrabutylammonium bromide.

**[0012]** The solvent to be used in the above step is not particularly restricted but includes, among others, acetone, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, dioxane and toluene. Among them, acetone, acetonitrile and N,N-dimethylformamide are preferred.

**[0013]** The carboxylic acid quaternary ammonium salt (3) is used generally in an amount of 1.0 to 2.0 moles, preferably 1.2 moles, per mole of the compound (1) or (2). The carboxylic acid metal salt (4) and quaternary ammonium salt (5) are used generally in a molar ratio of (1) or (2)/carboxylic acid metal salt/quaternary ammonium salt = 1.0 mole/1.0 to 5.0 moles/0.05 to 2.0 moles, preferably 1.0 mole/2.0 moles/0.05 mole.

**[0014]** The reaction is carried out generally at a temperature of 60°C to 100°C, preferably 60°C to 80°C. The reaction time is generally 5 to 24 hours, preferably about 10 to 12 hours, although it may vary depending on the reaction temperature.

**[0015]** After the reaction, the (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phenylbutane compound (6) formed can be recovered by extraction with a solvent such as ethyl acetate and can be further purified by such techniques as column

chromatography and/or recrystallization.

[0016] The sulfonic acid esterification of the (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phenylbutane compound (6) is carried out in the presence of an organic base by using 1.0 to 3 moles of a sulfonic acid halide per mole of the compound (6). The sulfonic acid halide includes, among others, sulfonyl chlorides, specifically methanesulfonyl chloride, toluenesulfonyl chloride and the like. As the organic base, there may be mentioned tertiary-amines, specifically pyridine, triethylamine, tripropylamine, methyldiisopropylamine, ethyldiisopropylamine, N,N-dimethylaniline and the like. Among them, pyridine and triethylamine are preferred. Any solvent not inhibiting the reaction may be used without any particular restriction. Thus, for example, toluene, acetone, acetonitrile, tetrahydrofuran, N,N-dimethylformamide, methylene chloride and chloroform may be mentioned. The organic base mentioned above may be used singly as such.

[0017] The base is used generally in an amount of 1.0 to 50 moles per mole of the compound (6). The reaction temperature is generally 0°C to 60°C, preferably 0°C to 25°C. The reaction time is generally 1 to 48 hours, desirably about 20 to 48 hours, although it may vary depending on the amounts of the sulfonic acid halide and base used.

[0018] The thus-formed sulfonate ester (7) can be recovered by neutralizing the base by addition of a mineral acid such as hydrochloric acid, followed by extraction with an organic solvent such as ethyl acetate. It can be further purified by such techniques as column chromatography and/or recrystallization.

[0019] The epoxidation step is conducted in the presence of an inorganic base. Useful as the inorganic base are, for example, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium acetate and potassium acetate. Potassium carbonate is preferred, however. The inorganic base is used generally in an amount of 0.05 to 5.0 moles, preferably 0.5 to 2.0 moles, per mole of the compound (7). Usable as the solvent are methanol plus an organic solvent such as toluene, tetrahydrofuran, diethyl ether, dioxane or t-butyl methyl ether. Methanol may be used alone. A mixed solvent composed of methanol and THF (1:1 by volume) is preferred. The reaction temperature is generally 0°C to 60°C, preferably 25°C to 30°C. The reaction time is generally 1 to 24 hours, preferably 6 to 12 hours.

## EXAMPLES

[0020] The following examples illustrate the present invention in further detail. They are, however, by no means limitative of the scope of the invention.

### Example 1 (2S, 3S)-1-Acetoxy-3-(t-butoxycarbonylamino)-2-hydroxy-4-phenylbutane

[0021] A mixture composed of 2.0 mmol (0.599 g) of (2S,3S)-3-(t-butoxycarbonylamino)-1-chloro-2-hydroxy-4-phenylbutane, 2.4 mmol (0.724 g) of tetrabutylammonium acetate and 10 ml of acetonitrile was stirred under reflux for 18 hours. Thereafter, the solvent was distilled off under reduced pressure, 20 ml of water and 20 ml of ethyl acetate were added, and the organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. This was dissolved in 10 ml of methanol with heating and the solution was cooled and allowed to stand. The resulting crystalline precipitate was collected by filtration, whereupon 0.449 g (70%) of the title compound was obtained.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.37 (s, 9H), 2.11 (s, 3H), 2.84-2.97 (m, 2H), 3.36 (br, 1H), 3.88-3.91 (m, 2H), 4.12 (dd, 1H, J = 11.7 Hz, 3.2 Hz), 4.59-4.76 (m, 1H), 7.20-7.32 (m, 5H).  
<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 20.92, 28.23, 36.01, 54.24, 66.24, 71.87, 80.01, 126.63, 128.57, 129.39, 137.42, 156.11, 171.34.

### Example 2 (2S,3S)-1-Acetoxy-3-(t-butoxycarbonylamino)-2-hydroxy-4-phenylbutane

[0022] A mixture composed of 2.0 mmol (0.524 g) of (2S,3S)-3-(t-butoxycarbonylamino)-4-phenylbutane-1,2-epoxide, 2.4 mmol (0.724 g) of tetrabutylammonium acetate, 4.0 mmol (0.24 g) of acetic acid and 10 ml of acetonitrile was stirred under reflux for 18 hours. Thereafter, the solvent was distilled off under reduced pressure, 20 ml of water and 20 ml of ethyl acetate were added, and the organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Purification by silica gel column chromatography gave 0.415 g (64%) of the title compound.

### Example 3 (2S,3S)-1-Acetoxy-3-(t-butoxycarbonylamino)-2-hydroxy-4-phenylbutane

[0023] A mixture composed of 2.0 mmol (0.599 g) of (2S,3S)-3-(t-butoxycarbonylamino)-1-chloro-2-hydroxy-4-phenylbutane, 0.1 mmol (0.032 g) of tetrabutylammonium bromide, 5.0 mmol (0.49 g) of potassium acetate and 10 ml of acetonitrile was stirred under reflux for 50 hours. Thereafter, the solvent was distilled off under reduced pressure, 20

ml of water and 20 ml of ethyl acetate were added, and the organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Quantitative analysis was carried out by high performance liquid chromatography using ethylbenzene as an internal standard. Thus was obtained 0.289 g (45%) of the title compound.

Example 4 (2S, 3S)-1-Acetoxy-3-(t-butoxycarbonylamino)-2-methanesulfonyloxy-4-phenylbutane

[0024] A mixture composed of 12.4 mmol (4.00 g) of (2S,3S)-1-acetoxy-3-(t-butoxycarbonylamino)-2-hydroxy-4-phenylbutane, 24.8 mmol (2.48 g) of methanesulfonyl chloride and 20 ml of pyridine was allowed to stand at 4°C for 48 hours. Thereafter, 30 ml of ethyl acetate was added, the organic layer was washed with three 30-ml portions of 10% hydrochloric acid and finally with 30 ml of water. The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. Hexane (30 ml) was added to the residue, and the mixture was allowed to stand. The resulting white solid precipitate was collected by filtration. Thus was obtained 4.90 g (98%) of the title compound.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.34 (s, 9H), 2.11 (s, 3H), 2.76 (m, 1H), 3.00 (dd, 1H, J = 4.9, 14.2 Hz), 3.11 (s, 3H), 4.15 (br, 1H), 4.21 (dd, 1H, J = 7.3, 12.7 Hz), 4.35-4.38 (m, 1H), 4.66-4.68 (m, 1H), 5.01 (br, 1H), 7.20-7.33 (m, 5H).  
<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 20.75, 28.15, 35.85, 38.72, 52.04, 62.96, 80.02, 80.82, 126.85, 128.63, 129.10, 136.55, 155.221, 170.27.

Example 5 (2R,3S)-3-(t-Butoxycarbonylamino)-4-phenylbutane 1,2-epoxide

[0025] A mixture composed of 1.0 mmol (0.401 g) of (2S,3S)-1-acetoxy-3-(t-butoxycarbonylamino)-2-methanesulfonyloxy-4-phenylbutane, 2.2 mmol (0.304 g) of potassium carbonate, 10 ml of methanol and 10 ml of tetrahydrofuran was stirred at 25°C for 20 hours. Thereafter, 10 ml of ethyl acetate and 10 ml of water were added for extraction of the product. The organic layer was separated, dried and the solvent was distilled off under reduced pressure to give a crude product. Purification by silica gel column chromatography gave 0.236 g (90%) of (2R,3S)-3-(t-Butoxycarbonylamino)-4-phenylbutane 1,2-oxirane.

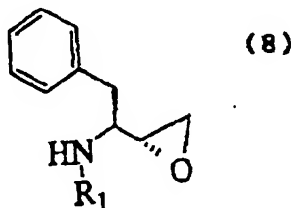
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.38 (s, 9H), 2.76-2.81 (m, 2H), 2.83-2.99 (m, 3H), 3.76 (br s, 1H), 4.45 (br, 1H), 7.21-7.33 (m, 5H).  
<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 28.26, 37.58, 46.91, 53.03, 53.20, 80.03, 126.68, 128.55, 129.46, 136.69, 155.21.

INDUSTRIAL APPLICABILITY

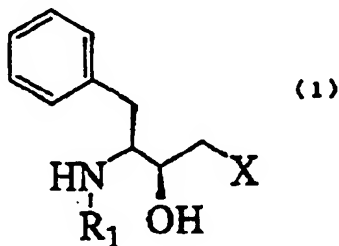
[0026] According to the present invention, it is possible to produce the desired (2R,3S)-3-amino-1,2-oxirane (8) efficiently via three steps from the (2S,3S)-3-amino-1-halo-2-hydroxy-4-phenylbutane compound (1) or (2S,3S)-3-amino-1,2-oxirane compound (2). The above starting compounds can be readily synthesized from L-phenylalanine. Thus, in other words, the (2S,3S)-3-amino-phenylbutane-1,2-epoxide compound (8) can be produced from L-phenylalanine.

Claims

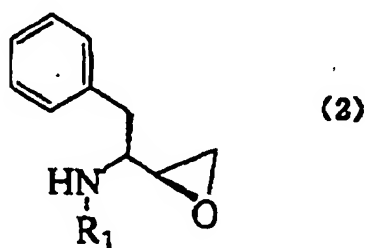
1. A process for producing (2R,3S)-3-amino-4-phenylbutane-1,2-epoxide compounds represented by the general formula (8):



wherein  $R_1$  represents an amino-protecting group, which comprises  
treating a (2S,3S)-3-amino-1-halo-2-hydroxy-4-phenylbutane compound represented by the general formula (1) or a (2S,3S)-3-amino-4-phenylbutane-1,2-epoxide represented by the general formula (2):



wherein  $R_1$  is as defined above and X represents a halogen atom,



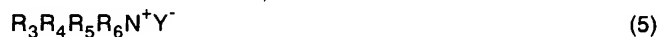
wherein  $R_1$  is as defined above,  
with a carboxylic acid quaternary ammonium salt represented by the general formula (3) or a carboxylic acid metal salt represented by the general formula (4):



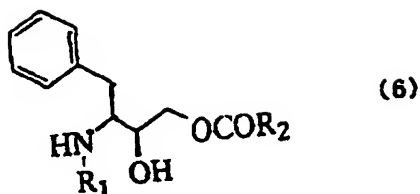
wherein  $R_2$  represents an alkyl, aryl or aralkyl group and  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  may be the same or different and each independently represents an alkyl or aralkyl group,



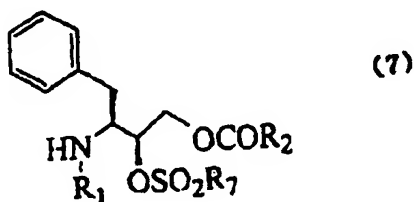
wherein  $R_2$  is as defined above and M represents a metal atom, and a quaternary ammonium salt represented by the general formula (5):



wherein  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are as defined above and Y represents a halogen atom,  
to give a (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phenylbutane compound represented by the general formula (6):



10 wherein  $R_1$  and  $R_2$  are as defined above,  
 further treating said (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phenylbutane compound with a sulfonic acid  
 halide in the presence of an organic base,  
 to give a (2S,3S)-1-acyloxy-3-amino-2-sulfonyloxy-4-phenylbutane compound represented by the general formula  
 (7) :



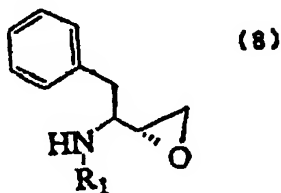
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25 wherein  $R_1$  and  $R_2$  are as defined above and  $R_7$  represents an alkyl, aryl or aralkyl group,  
 furthermore treating said (2S,3S)-1-acyloxy-3-amino-2-sulfonyloxy-4-phenylbutane compound with an inor-  
 ganic base.

- 30
2. The process for producing according to Claim 1,  
 wherein the compound of the general formula (3) is tetrabutylammonium acetate.
  3. The process for producing according to Claim 1,  
 wherein the compound of the general formula (4) is potassium acetate or sodium acetate and  
 the compound of the general formula (5) is tetrabutylammonium chloride or tetrabutylammonium bromide.
  - 35 4. The process for producing according to any of Claims 1, 2 and 3,  
 wherein  $R_1$  is a t-butoxycarbonyl group or benzyloxycarbonyl group and  
 X is a chlorine atom.
  - 40 5. The process for producing according to any of Claims 1, 2, 3 and 4,  
 wherein the sulfonic acid halide is methanesulfonyl chloride or toluenesulfonyl chloride.

#### 45 Patentansprüche

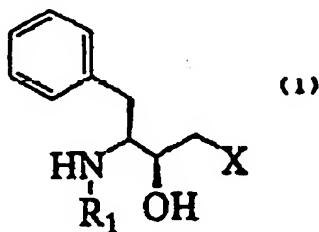
1. Verfahren zur Herstellung von (2R,3S)-3-Amino-4-phenylbutan-1,2-epoxid-Verbindungen der allgemeinen Formel  
 (8):



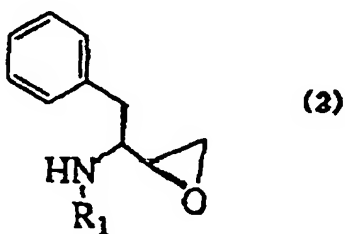


wobei  $R_1$  eine Aminoschutzgruppe darstellt,  
welches umfasst:

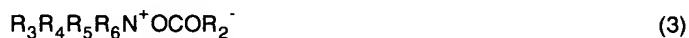
Behandeln einer (2S,3S)-3-Amino-1-halo-2-hydroxy-4-phenylbutan-Verbindung der allgemeinen Formel (1) oder  
eines (2S,3S)-3-Amino-4-phenylbutan-1,2-Epoxids der allgemeinen Formel (2)



wobei  $R_1$  wie vorstehend definiert ist und X ein Halogenatom darstellt,



wobei  $R_1$  wie vorstehend definiert ist,  
mit einem quaternären Ammoniumsalz einer Carbonsäure der allgemeinen Formel (3) oder einem Carbonsäure-  
metallsalz der allgemeinen Formel (4):



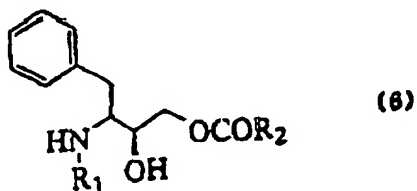
wobei  $R_2$  einen Alkyl-, Aryl- oder Aralkylrest darstellt und  $R_3$ ,  $R_4$ ,  $R_5$  und  $R_6$  gleich oder verschieden sein können  
und jeweils unabhängig einen Alkyl- oder Aralkylrest darstellen,



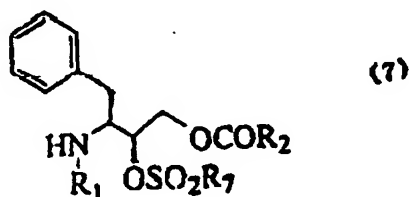
wobei  $R_2$  wie vorstehend definiert ist und M ein Metallatom darstellt, und einem quaternären Ammoniumsalz der  
allgemeinen Formel (5):



wobei  $R_3$ ,  $R_4$ ,  $R_5$  und  $R_6$  wie vorstehend definiert sind und Y ein Halogenatom darstellt, um eine (2S,3S)-1-Acyloxy-  
3-amino-2-hydroxy-4-phenylbutan-Verbindung der allgemeinen Formel (6) zu ergeben:



wobei  $R_1$  und  $R_2$  wie vorstehend definiert sind, Weiterbehandeln der (2S,3S)-1-Acyloxy-3-amino-2-hydroxy-4-phenylbutan-Verbindung mit einem Sulfonsäurehalogenid in Gegenwart einer organischen Base, um eine (2S,3S)-1-Acyloxy-3-amino-2-sulfonyloxy-4-phenylbutan-Verbindung der allgemeinen Formel (7) zu ergeben:

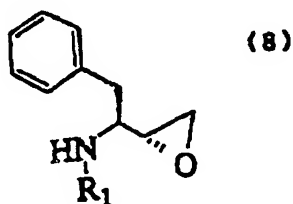


wobei  $R_1$  und  $R_2$  wie vorstehend definiert sind und  $R_7$  einen Alkyl-, Aryl- oder Aralkylrest darstellt, Weiterbehandeln der (2S,3S)-1-Acyloxy-3-amino-2-sulfonyloxy-4-phenylbutan-Verbindung mit einer anorganischen Base.

2. Herstellungsverfahren nach Anspruch 1, wobei die Verbindung der allgemeinen Formel (3) Tetrabutylammoniumacetat ist.
3. Herstellungsverfahren nach Anspruch 1, wobei die Verbindung der allgemeinen Formel (4) Kaliumacetat oder Natriumacetat ist, und die Verbindung der allgemeinen Formel (5) Tetrabutylammoniumchlorid oder Tetrabutylammoniumbromid ist.
4. Herstellungsverfahren nach einem der Ansprüche 1, 2 und 3, wobei  $R_1$  ein t-Butoxycarbonylrest oder ein Benzylloxycarbonylrest ist, und X ein Chloratom darstellt.
5. Herstellungsverfahren nach einem der Ansprüche 1, 2, 3 und 4, wobei das Sulfonsäurehalogenid Methansulfonylchlorid oder Toluolsulfonylchlorid ist.

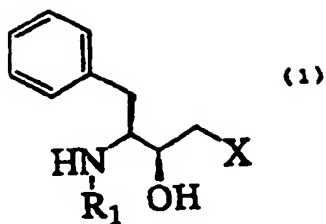
#### Revendications

1. Procédé pour la production de composés du (2R,3S)-3-amino-4-phénylbutane-1,2-époxyde représentés par la formule générale (8) :

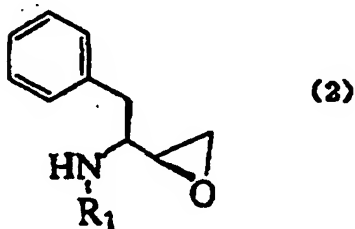


où  $R_1$  représente un groupe protecteur d'amino, qui comprend

le traitement d'un composé de (2S,3S)-3-amino-1-halogéno-2-hydroxy-4-phénylbutane représenté par la formule générale (1) ou du (2S,3S)-3-amino-4-phénylbutane-1,2-époxyde représenté par la formule générale (2) :



10 où R<sub>1</sub> est tel que défini ci-dessus et X représente un atome d'halogène,



25 où R<sub>1</sub> est tel que défini ci-dessus,

avec un sel d'ammonium quaternaire d'un acide carboxylique représenté par la formule générale (3) ou un sel de métal d'un acide carboxylique représenté par la formule générale (4) :



où R<sub>2</sub> représente un groupe alkyle, aryle ou aralkyle et R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> et R<sub>6</sub> peuvent être identiques ou différents et chacun représente de façon indépendante un groupe alkyle ou aralkyle,

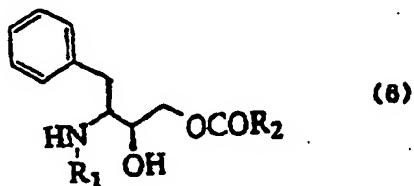


où R<sub>2</sub> est tel que défini ci-dessus et M représente un atome métallique, et un sel d'ammonium quaternaire représenté par la formule générale (5) :



où R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> et R<sub>6</sub> sont tels que définis ci-dessus et Y représente un atome d'halogène, pour obtenir un composé de (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phénylbutane représenté par la formule générale (6)

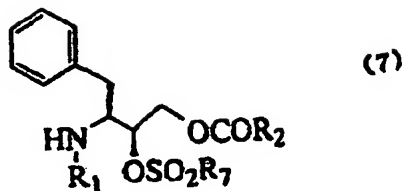
45



55 où R<sub>1</sub> et R<sub>2</sub> sont tels que définis ci-dessus,

puis le traitement dudit composé de (2S,3S)-1-acyloxy-3-amino-2-hydroxy-4-phénylbutane par un halogénure d'acide sulfonique en présence d'une base organique, pour obtenir un composé de (2S,3S)-1-acyloxy-3-amino-2-sulfonyloxy-4-phénylbutane représenté par la formule

générale (7) :



où  $R_1$  et  $R_2$  sont tels que définis ci-dessus, et  $R_7$  représente un groupe alkyle, aryle ou aralkyle,  
 puis le traitement dudit composé de (2S,3S)-1-acyloxy-3-amino-2-sulfonyloxy-4-phénylbutane par une base  
 minérale.

- 15
2. Procédé de production selon la revendication 1, dans lequel le composé de formule générale (3) est l'acétate de  
 tétrabutylammonium.
- 20
3. Procédé de production selon la revendication 1, dans lequel le composé de formule générale (4) est l'acétate de  
 potassium ou l'acétate de sodium et le composé de formule générale (5) est le chlorure de tétrabutylammonium  
 ou le bromure de tétrabutylammonium.
- 25
4. Procédé de production selon l'une quelconque des revendications 1, 2 et 3, dans lequel  $R_1$  est un groupe t-bu-  
 toxycarbonyl ou un groupe benzyloxycarbonyl et X est un atome de chlore.
5. Procédé de production selon l'une quelconque des revendications 1, 2, 3 et 4, dans lequel l'halogénure d'acide  
 sulfonique est le chlorure de méthanesulfonyl ou le chlorure de toluènesulfonyl.